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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,051	02/26/2004	Arthur M. Krieg	C1039.70083US06	8295

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,051	KRIEG ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,31-35 and 37-47* is/are pending in the application.

4a) Of the above claim(s) *34,38 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,31-33,35,37,39,40 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/18/08 has been entered.

Claims 28, 31-35, 37-47 are pending in the application. Claims 28, 31-33, 35, 37, 39-40, and 42-47 are under examination.

Rejections Maintained

1) The rejection of claims 28, 31-33, 35, 37, 39, 40, 42, 43-46 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 36 of copending Application No. 10/787,737 is maintained for reasons made of record in the previous office action. Applicant has elected to defer rebuttal of this rejection.

2) The rejection of claims 28, 31-33, 35, 37, 39, 40 and 42-47 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons made of record in the previous office actions filed 3/22/07 and 1/18/2008.

The claims are drawn to a method for treating or preventing an immune system deficiency, comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to treat the immune system deficiency, wherein the oligonucleotide is stabilized, wherein the oligonucleotide comprises 5'-TGACGTT-3' wherein the oligonucleotide comprises a phosphorothioate modification wherein the immune system deficiency is due to a cancer, viral infection or a bacterial infection.

The specification only defines an immune system deficiency to mean:

A disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small' cell), ovary breast, prostate, colon as well as carcinomas and sarcomas) or viral (e.g. HIV, herpes), fungal (e.g. Candida sp.), bacterial or parasitic (e.g. Leishmania, Toxoplasma) infection in a subject.

See p. 11 lines 21 to 26 of the specification.

The instant specification does not teach which immune system deficiencies are due to the extremely broad scope of the different types of cancers, the different types of viral infection or the different types of bacterial infections.

As set forth in the previous actions, the scope of immune system deficiency is broad and includes severe combined immunodeficiency syndrome, cell mediated immunity deficiency syndromes, X-linked agammaglobulinaemia, antibody deficiency syndrome (see Herbet et al, The Dictionary of Immunology, page 89, cited previously). Severe combined immunodeficiency is a disease in which both humoral and cell-mediated immunity are defective. In X-linked agammaglobulinaemia, there are low numbers of circulating B cells (i.e. mature) and

of all immunoglobulin. Pre-B lymphocytes are present in normal numbers of the bone marrow. In this disease there is a single defect in a single gene encoding a protein tyrosine kinase. Cell mediated immunity deficiency syndromes are characterized by failure to express reactions of cell-mediated immunity (i.e. to reject an allograft, become sensitized to agents causing contact hypersensitivity, show delayed-type hypersensitivity reactions) and example include DiGeorge's syndrome, thymic hypoplasia and SCID. Antibody deficiency syndrome is characterized by low serum immunoglobulin levels and failure to produce antibody normally upon antigenic challenge. One, two or all three of the major classes of immunoglobulin (IgG, IgA and IgM) may be deficient. Antibody deficiency may exist in the presence of normal cell-mediated immunity. Types of antibody deficiencies are common variable immunodeficiency, IgA deficiency, IgG subclass deficiencies, X-linked agammagloublinaemia and X-linked hyper-IgM syndrome (see Herbet et al, The Dictionary of Immunology, pages 10, 33,141 and 166, cited previously).

The instant specification does not teach which of these immune system deficiencies are due to cancer, viral infection or bacterial infection. Immune system deficiencies such as the primary deficiencies described above are caused by intrinsic or genetic defects in the immune system. The art does not recognize the prevention of such intrinsic or genetic defects in the immune system. However, therapeutic methods are available for primary immune system deficiencies and are geared towards immunoglobulin replacement therapy, haematopoietic stem cell transplantation (using bone marrow, cord blood or peripheral blood) and gene therapy (Cunnigham et al. 2005. Nature Review Immunology vol. 5 p.880-892, cited previously).

The specification as of the time of filing does not provide empirical data showing efficacy of the instant oligonucleotide in any art- recognized model of immunodeficiency due to any cancer or viral or bacterial infection.

The teachings of the specification are limited to *in vitro* data that demonstrate that unmethylated cytosine –guanine containing oligonucleotides stimulate B-cells and induce the production of cytokines and in vivo data that demonstrates in vivo induction of IL-6 in mice injected with said oligonucleotides. Production of IgM, natural killer cell activity and IL-6 by administering specific oligos containing the CpG DNA segment is not the same as any and/or all therapeutic effects (treating, preventing, ameliorating) in any and/or all subjects having an immune system deficiency which is broadly defined in the instant specification as a disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response such as to eliminate a tumor or cancer of brain , lung, ovary, breast, prostate, colon etc, or viral, fungal, bacterial or parasitic infection in a subject. The specification at the time of filing does not correlate the immune responses generated with treatment or prevention of immune system deficiency due to cancer or viral or bacterial infection. As to an immune system deficiency due to a virus e.g. HIV, as at the time of filing, many questions existed about how the HIV virus caused immunodeficiency (AIDS) and how HIV can deplete CD4 positive T lymphocytes and cause AIDS (James, J.S. AIDS Treatment News No. 147- March 20, 1992). Thus, for an immune system deficiency such as AIDS for which the pathogenesis is unclear, it is unpredictable that the instant oligonucleotide can treat or prevent AIDS. The instant specification does not correlate the immune responses generated by the instant oligonucleotide with treatment or prevention of AIDS due to HIV.

The specification as filed does provide guidance or direction as to the other immune system deficiencies due to or caused by other viruses or due to or caused by cancer or due to or caused by bacterial infection and does not correlate the immune responses to the instant oligonucleotide with treatment or prevention of immune system deficiency due to viruses or due to cancer or due to bacterial infection and one of skill in the art would not how to use the invention as claimed.

In the reply to the previous office action of 3/22/07, Applicant cited two papers by Gramzinski et al (Infection and Immunity v. 69 March 2001 p. 1643-1649) and by Jeamwattanalert et al (Clinical and Vaccine Immunology, April 2007, p.342-347) to show support for treatment and prevention of parasitic infection. Applicants argued that Gramzinski describes the use of CpG ODN to prevent malaria infection in mice and that it was determined that the ability of CpG ODN to confer this protection was dependent on the ability to induce IL-12 and IFN-gamma and that the teachings of Gramzinski are consistent with the specification. Further Applicants argue that Jeamwattanalert et al teaches a study drawn towards the immunization of mice against a malarial antigen using CpG ODN as an adjuvant and that there was long lasting protective immune response to a *Plasmodium yoelli* antigen in mice.

Applicants now argue that the papers were cited to show the beneficial effects of CpG oligonucleotides in a parasitic infection. These papers are still not persuasive to overcome the instant rejection and are directed to subject matter not within the scope of the claims. The instant claims are now drawn to treatment or prevention of an immune system deficiency due to a cancer or a virus or a bacterial infection. The scope of the claims do not encompass treatment of parasitic infection but treatment of immune system deficiency due to cancer or viral or bacterial

infection. In addition, the CpG ODN of Gramzinski and Jeamwattanalert are different sequences from the one being used in the instant invention. The CpG ODN of Gramzinski and Jeamwattanalert is 20 base pairs in length with a particular base sequence and it is this CpG ODN that confers protection in the case of Gramzinski and acts as an adjuvant in the case of Jeamwattanalert.

Applicants argue that mice models are acceptable for studying CpG oligonucleotides because numerous scientific articles have been published on the use of CpG oligonucleotides in animal models including mice and that the scientific community must find mouse models of CpG oligonucleotides to provide acceptable teachings. This argument is carefully considered but is not found persuasive. The Gramzinski and Jeamwattanalert do not disclose the instant oligonucleotide comprising 5'-TGACGTT-3' and the scope of the claims do not encompass treatment of parasitic infection but treatment of immune system deficiency due to cancer or viral or bacterial infection. Although, mice models are routinely used to study many different therapies including CpG oligonucleotides, studies in mice do not often predict efficacy in humans. For example, the art teaches that it is difficult at best to use observations with CpG ODNs in murine studies to predict accurately the effects of TLR9 (cellular receptor for CpG ODN) activation in humans because the cellular patterns of TLR expression vary between species so the results of TLR stimulation (in mice, for example) may not be predictive of what will occur in another (humans) (Krieg et al. Proc Am Thorac Soc vol. 4 p. 289-294, 2007, see p. 289 left column under *the role of TLR9 in the mechanism of action of CpG ODNs*).

The instant specification has not provided any correlation between immunostimulatory properties of the instant CpG ODN and the treatment or prevention of any immune system deficiency due to any cancer or any virus or any bacterial infection.

Applicants argue that the Sfondiri et al reference FASEB 2002 vol. 16 p. 1749-1754) provided by Applicants does provide for an oligonucleotide ODN 1668 that includes TGACGTT. Applicants are correct. Sfondiri et al does teach that phosphorothioate modified ODN 1668 prevented the development of spontaneous mammary tumors in 4 out of 11 mice after 380 days (FVB-NeuN transgenic mice were treats i.p. with CpG ODN every 10 days starting at 10 wk of age) while all untreated mice developed mammary tumors before 305 days of age (p. 1750 under oligonucleotides and under results and p. 1751 fig. 1). However, the results of Sfondiri are limited to treatment or prevention of one type of (cancer mammary adenocarcinoma tumors) while the instant claims are drawn to treating or preventing any immune system deficiency due to any type of cancer. Further, the results obtained are in a mice model. As mentioned above, the art teaches that it is difficult at best to use observations with CpG ODNs in murine studies to predict accurately the effects of TLR9 (cellular receptor for CpG ODN) activation in humans because the cellular patterns of TLR expression vary between species so the results of TLR stimulation (in mice, for example) may not be predictive of what will occur in another (humans) (Krieg et al. Proc Am Thorac Soc vol. 4 p. 289-294, 2007, see p. 289 left column under *the role of TLR9 in the mechanism of action of CpG ODNs*).

In addition, conditions for treating the mice already having the mammary adenocarcinoma tumors varied. In mice bearing small spontaneous mammary tumors, no significant tumor inhibition (treatment of tumors) was observed using increased i.p. doses and

increased frequency of administration whereas significant inhibition was observed when 40 ug of the CpG ODN were injected at the tumor site for 5 days (p. 1751 column 2 first complete paragraph). Sfondiri et al further demonstrates the complexity of treating the tumors in mice. Mice inoculated i.v. with N202.1A carcinoma cells formed significantly fewer lung metastases after 4 wk if treated with CpG ODNs (20 ug/mouse) 4h before or 2h after tumor cell inoculation compared with control and mice administered 40 ug CpG ODN administered i.p. 4 hours before and in the 4 subsequent days had inhibition of experimental metastases although still incomplete. No inhibitory effect was observed when CpG-ODN was administered 48 h after N202.1A cell injection. Thus, in addition to the fact that it is it is difficult at best to use observations with CpG ODNs in murine studies to predict accurately the effects of TLR9 (cellular receptor for CpG ODN) activation in humans, it is clear that even in mice, the treatment of one type of cancer i.e. mammary adenocarcinoma with phosphorothioate CpG ODN comprising TGACGTT is complex and is dose, route and schedule of treatment dependent. It is art recognized that for any novel therapy, the transition from the laboratory to the clinic (Petri dish experiments to animal experiments to bedside) is a quantum leap (Chatterjee et al. Cancer Immunol Immunother. 1994 38:75-82). Results obtained with CPG treatments under controlled conditions in mice often differ from the clinical response obtained in patients (Krieg et al. Proc Am Thorac Soc vol. 4 p. 289-294, 2007). Since the therapeutic indices of immunotherapeutic regimens can be species and model dependent it is not clear that reliance on the *in vitro* and *in vivo* stimulation of B cells with unmethylated cytosine guanine oligonucleotides accurately reflects the efficacy of the claimed therapeutic strategy or prevention strategy based upon *in vitro* stimulation as disclosed in the specification. One of skill in the art at the time of filing could not

predict the efficacy of phosphorothioate modified unmethylated cytosine guanine containing oligonucleotide comprising 5'-tgacgtt- 3'for the treatment and prevention of immune system deficiencies due to *all* types of cancer, *any* type of viral infection or *any* type of bacterial infection. The Gura et al reference (cited previously) shows the state of the art as to the paucity of the use of CpG ODN in humans for the treatment or prevention of any disease or disorder due to an immune system deficiency at the time of filing of the instant invention which has priority to 1994.

Reasonable correlation must exist between the scope of the claims and the enablement set forth. In view of the absence of working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would require undue experimentation to practice the invention as claimed.

The specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

As to the Krieg et al reference (J. Clin. Investigation, 2007, v. 117, p. 1184), Applicants argue that the reference shows CpG oligonucleotides being used in combination with vaccines as well as with chemotherapies and other therapies and that the studies described are human clinical trials. Applicants argue that the claims encompass the use of CpG oligonucleotides alone or in combination with other therapies and that the data described in Krieg is presented to rebut the assertion that oligonucleotides are not useful in the treatment of cancer.

This is carefully considered but not persuasive. The instant claims do not encompass the use of CpG oligonucleotides in combination with other therapies. The claims recite "a method for

treating or preventing an immune system deficiency, comprising administering to a subject *an* oligonucleotide containing an unmethylated cytosine-guanine to treat the immune system deficiency, wherein the oligonucleotide is stabilized, wherein the oligonucleotide comprises 5'-TGACGTT-3' wherein the oligonucleotide comprises a phosphorothioate modification wherein the immune system deficiency is due to a cancer, viral infection or a bacterial infection."

The instant method administers to a subject *an* oligonucleotide containing an unmethylated cytosine-guanine. The only thing being administered is the instant oligonucleotide and nothing else. Although Krieg et al discloses CpG ODN as monotherapy in human clinical trials for treatment of specific cancers (see table 2 compound PF-3512676 aka CPG 7909 when formulated without an adjuvant) Krieg does not disclose the instant oligonucleotide comprising 5'-TGACGTT-3'.

The breadth of the instant claims is extremely broad. The breadth of cancer, viral infection or bacterial infection is extremely broad. The specification does not set forth and describe the immune system deficiencies due to all cancers or all viral infections or all bacterial infections. The specification as of the time of filing does not correlate the immune responses generated by the instant product with treatment or prevention of an immune system deficiency due to any cancer or any viral infection or any bacterial infection and for the reasons above undue experimentation would be required of the skilled artisan to use the invention as claimed.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 31-33, 35, 37, 39, 40 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are drawn to a method for treating or preventing an immune system deficiency, comprising administering to a subject an oligonucleotide containing an unmethylated cytosine-guanine to treat the immune system deficiency, wherein the oligonucleotide is stabilized, wherein the oligonucleotide comprises 5'-TGACGTT-3' wherein the oligonucleotide comprises a phosphorothioate modification wherein the immune system deficiency is due to a cancer, viral infection or a bacterial infection.

The instant claims now recite that the immune system deficiency is due to a cancer, viral infection or a bacterial infection. The instant specification does not disclose immune system deficiency is due to a cancer, viral infection or a bacterial infection or describe any particular immune system deficiencies due to a cancer, viral infection or a bacterial infection. The specification only defines an immune system deficiency to mean:

A disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small' cell), ovary breast, prostate, colon as well as carcinomas and sarcomas) or viral (e.g. HIV, herpes), fungal (e.g. Candida sp.), bacterial or parasitic (e.g. Leishmania, Toxoplasma) infection in a subject.

See p. 11 lines 21 to 26 of the specification.

Thus, the specification does not teach that an immune system deficiency ***is due*** to a cancer, viral infection or a bacterial infection but instead teaches disease or disorder that would be useful to boost an immune response to ***eliminate*** cancer or viral or bacterial infection in a subject. An immune system deficiency as defined by the specification means that the subject's immune system is not functioning in normal capacity or boosting of a subject's immune response.

Applicant can overcome this rejection by pointing the specification by page number and line number for where support exists for 'immune system deficiency *due* to a cancer, viral infection or a bacterial infection.

Status of Claims

Claims 28, 31-33, 35, 37, 39, 40 and 42-47 are rejected. No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am – 5:00 pm. If attempts to reach the examiner

by telephone are unsuccessful, the examiner's Supervisor Shanon Foley (571-272-0898) or Robert Mondesi (571-272-0956) can be contacted .

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Oluwatosin Ogunbiyi/

Examiner, Art Unit 1645

/Patricia A. Duffy/

Primary Examiner, Art Unit 1645